NOVEL USEFUL THERAPEUTIC AGENT FOR LOWER URINARY TRACT SYMPTOM

Provided is a therapeutic agent for lower urinary tract symptom consisting of (+)-3-{1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl}-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof or a combination of (+)-3-{1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl}-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof and a compound selected from the group consisting of α₁-adrenergic receptor blockers, 5-α-reductase inhibitors, antiandrogen drugs, β₃-adrenergic receptor agonists, phosphodiesterase V inhibitors, plant preparations, amino acid preparations, herbal medicines and the like. Also provided is a method of using in combination the above-described therapeutic agent and a surgical treatment such as bladder distention or surgery.
Description

Technical Field

[0001] The present invention relates to a novel useful therapeutic agent for lower urinary tract symptoms.

Background Art

[0002] Lower urinary tract symptoms generally refer to symptoms caused by a wide variety of diseases such as benign prostatic hyperplasia and interstitial cystitis, including urine storage symptoms such as increased daytime frequency, nocturia, urinary urgency, urge urinary incontinence, stress urinary incontinence, and mixed urinary incontinence; voiding symptoms such as slow stream, weak urine streams, and urine stream intermittency; post-micturition symptoms such as feeling of incomplete emptying and post-micturition drips; lower urinary tract pains such as bladder pain and urethral pain; and the like. Also included is overactive bladder syndrome, which an urinary urgency is essential, and, either urge urinary incontinence is present or absent, and accompanied by increased daytime frequency and nocturia (see Non-patent Document 1). The prevalence rate of lower urinary tract symptoms increases with age; it has been reported that about 80% of people 60 years or older have some lower urinary tract symptoms (see Non-patent Document 2).

In benign prostatic hyperplasia, not only urinary retention (voiding symptoms, post-micturition symptoms) due to urethral obstruction occur as lower urinary tract symptoms, but also urine storage symptoms such as increased daytime frequency, nocturia, and urinary urgency are often coincidental. Widely prescribed as therapeutic drugs for benign prostatic hyperplasia, α₁-adrenergic receptor blockers and 5-α reductase inhibitors ameliorate voiding symptoms and post-micturition symptoms by reducing urethral resistance, but they are hardly effective on overactive bladder symptoms, which are characterized by the complaint of urinary urgency. Therefore, in the treatment of these overactive bladder symptoms, in addition to α₁-adrenergic receptor blockers, antimuscarinic drugs are used in combination (see Non-patent Document 3).

Although antimuscarinic drugs such as solifenacin, toterodine, oxybutynin, propiverine, darifenacin, imidafenacin, trospium, and fesoterodine exhibit a certain effect on lower urinary tract symptoms such as increased daytime frequency and urinary incontinence by blocking the muscarine receptors expressed in the detrusor smooth muscle, they do not have a sufficient ameliorating effect on urinary urgency, which is considered to occur due to activation of the afferent nerve of the urinary bladder (mainly C-fiber).

[0003] Meanwhile, a preparation comprising (+)-3-{1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl}-4-phenyl-3,4-dihydro-2(1H)-quinazolinone, that is, the compound represented by the following formula (1):

[0004]

![Chemical Structure](image)

[0005] or a pharmaceutically acceptable salt thereof, as an active ingredient, possesses both antimuscarinic action and C-fiber-suppressing action, and is therefore thought to be effective on lower urinary tract symptoms such as increased daytime frequency, nocturia, urinary urgency, urge urinary incontinence, mixed urinary incontinence, bladder pain, and urethral pain when used alone, and to be more effective when used in combination with an α₁-adrenergic receptor blocker, a 5-α reductase inhibitor, an antiandrogen drug, a β₃-adrenergic receptor agonist, a phosphodiesterase V inhibitor, a plant preparation, an amino acid preparation, a herbal medicine, an intravesical instillation or detrusor injection therapy, a serotonin-norepinephrine reuptake inhibitor, a selective serotonin reuptake inhibitor, a selective norepinephrine reuptake inhibitor, a tricyclic antidepressant drug, an α₂-adrenergic receptor agonist, female hormone replacement therapy, a surgical therapy, a urinary bladder intima protecting agent, an antiallergic drug, an antihistamine drug, a steroid or bladder distention (see Patent Document 1).

[Summary of the Invention]

Problems to Be Solved by the Invention

[0006] Currently available therapeutic methods for lower urinary tract symptoms such as increased daytime frequency, nocturia, urgent urinary urgency, urge urinary incontinence, mixed urinary incontinence, bladder pain, and urethral pain include antimuscarinic drugs, α1-adrenergic receptor blockers, 5α-reductase inhibitors, antiandrogenic drugs, β2-adrenergic receptor agonists, phosphodiesterase V inhibitors, plant preparations, amino acid preparations, herbal medicines, intravesical instillation or detrusor injection therapy, β3-adrenergic receptor agonists, serotonin-norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, tricyclic antidepressant drugs, α-adrenergic receptor agonists, female hormone replacement therapy, surgical therapies, urinary bladder intima protecting agents, antiallergic drugs, antihistamine drugs, steroids, bladder distention and the like; however, in not a few cases, these therapies fail to have a sufficient therapeutic effect when used alone (see Chapple CR., European Urology, 49, 651, 2006).

It is an object of the present invention to provide a therapeutic agent for lower urinary tract symptom that ensures a sufficient therapeutic effect.

Means of Solving the Problems

[0007] The present inventors conducted extensive investigations to find a novel useful therapeutic method for lower urinary tract symptoms, found that a preparation comprising as an active ingredient the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof, which is a therapeutic drug for overactive bladder syndrome, possesses a suppressing action on the action to raise the membrane potential, which is an indicator of neuron excitement, that is, possesses C-fiber activation-suppressing action, in an investigation with the use of C-fiber-derived small DRG neurons, and that the same preparation possesses a more potent suppressing action when used in combination with an α1-adrenergic receptor blocker when than used alone, and that have completed the present invention.

[0008] Accordingly, the present invention relates to the following:

1. A therapeutic agent for lower urinary tract symptom comprising (+)-3-[[3-(trifluoromethoxy)benzyl]piperidin-4-yl]-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof as an active ingredient.

2. A therapeutic agent for lower urinary tract symptom comprising a combination of (+)-3-[[3-(trifluoromethoxy)benzyl]piperidin-4-yl]-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof, and a drug selected from the group consisting of a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence and a therapeutic agent for interstitial cystitis/painful bladder syndrome.

3. A therapeutic agent for lower urinary tract symptom comprising a combination of (+)-3-[[3-(trifluoromethoxy)benzyl]piperidin-4-yl]-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof, and a drug selected from the group consisting of an α1-adrenergic receptor blocker, a 5α-reductase inhibitor, a β3-adrenergic receptor agonist, a phosphodiesterase V inhibitor, a plant preparation, an amino acid preparation, a female hormone, a herbal medicine, an intravesical instillation or detrusor injection therapy, a β2-adrenergic receptor agonist, a serotonin-norepinephrine reuptake inhibitor, a selective serotonin reuptake inhibitor, a tricyclic antidepressant drug, an α-adrenergic receptor agonist, a female hormone, a urinary bladder intima protecting agent, an antiallergic drug, an antihistamine drug and a steroid.

4. The therapeutic agent for lower urinary tract symptom described in [2], wherein the therapeutic agent for benign prostatic hyperplasia is an α1-adrenergic receptor blocker.

5. The therapeutic agent for lower urinary tract symptom described in [2], wherein the α1-adrenergic receptor blocker is selected from the group consisting of naftopidil and tamsulosin.

6. The therapeutic agent for lower urinary tract symptom described in [2], wherein the therapeutic agent for benign prostatic hyperplasia is a 5α-reductase inhibitor.

7. The therapeutic agent for lower urinary tract symptom described in [2], wherein the therapeutic agent for benign prostatic hyperplasia is an antiandrogen drug.

8. The therapeutic agent for lower urinary tract symptom described in [2], wherein the therapeutic agent for overactive bladder syndrome is a β3-adrenergic receptor agonist.

9. The therapeutic agent for lower urinary tract symptom described in [8], wherein the β3-adrenergic receptor agonist...
is a selective β3-adrenergic receptor agonist.

[10] The therapeutic agent for lower urinary tract symptom described in [2], wherein the therapeutic agent for overactive bladder syndrome or the therapeutic agent for benign prostatic hyperplasia is a phosphodiesterase V inhibitor.

[11] The therapeutic agent for lower urinary tract symptom described in [2], wherein the therapeutic agent for benign prostatic hyperplasia is a plant preparation, an amino acid preparation, or a herbal medicine.

[12] A combination therapy with (+)-3-{1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl}-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof, and vesical instillation of resiniferatoxin or capsaicin or urinary bladder wall injection of botulinum toxin, for treating lower urinary tract symptoms.

[13] The therapeutic agent for lower urinary tract symptom described in [2], wherein the therapeutic agent for stress urinary incontinence is a β3-adrenergic receptor agonist.

[14] The therapeutic agent for lower urinary tract symptom described in [2], wherein the therapeutic agent for stress urinary incontinence is a serotonin-norepinephrine reuptake inhibitor, a selective serotonin reuptake inhibitor, or a selective norepinephrine reuptake inhibitor.

[15] The therapeutic agent for lower urinary tract symptom described in [2], wherein the therapeutic agent for stress urinary incontinence or the therapeutic agent for pollakiuria/urinary incontinence is a tricyclic antidepressant drug.

[16] The therapeutic agent for lower urinary tract symptom described in [2], wherein the therapeutic agent for stress urinary incontinence is an α-adrenergic receptor agonist.

[17] A combination therapy with (+)-3-{1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl}-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof, and a surgery for treating benign prostatic hyperplasia, for treating lower urinary tract symptoms.

[18] A combination therapy with (+)-3-{1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl}-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof, and a female hormone replacement therapy, for treating lower urinary tract symptoms.

[19] A combination therapy with (+)-3-[1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl]-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof, and an interstitial cystitis/painful bladder syndrome therapy, for treating lower urinary tract symptoms.

Effect of the Invention

[0009] A preparation comprising as an active ingredient the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof, which is a novel therapeutic drug for overactive bladder, possesses both antimuscarinic action and C-fiber-suppressing action, and becomes a novel useful therapeutic agent for lower urinary tract symptom not only when used alone, but also when used in combination with an α1-adrenergic receptor blocker, a 5-α reductase inhibitor, an antiandrogen drug, a β3-adrenergic receptor agonist, a phosphodiesterase V inhibitor, a plant preparation, an amino acid preparation, a herbal medicine, an intravesical instillation or detrusor injection therapy, a β2-adrenergic receptor agonists, serotonin-norepinephrine reuptake inhibitor, a selective serotonin reuptake inhibitor, a selective norepinephrine reuptake inhibitor, a tricyclic antidepressant drug, an α-adrenergic receptor agonist, a female hormone replacement therapy, a surgical therapy, a urinary bladder intima protecting agent, an antiallergic drug, an antihistamine drug, a steroid or bladder distention.

Brief Description of the Drawings

[0010]

Fig. 1 shows an effect of the compound A on membrane potential when used alone.

Fig. 2 shows effects of naftopidil on membrane potential when used alone and when used in combination with the compound A.

Fig. 3 shows effects of tamsulosin on membrane potential when used alone and when used in combination with the compound A.

[Modes for Embodying the Invention]

[0011] The present invention is hereinafter described in more detail.

[0012] A preparation comprising as an active ingredient the compound represented by the formula (1) or a pharmaceutically acceptable salt thereof, which is an active ingredient of a pharmaceutical composition in the present invention,
exhibits an excellent ameliorating effect on lower urinary tract symptoms, not only when used alone, but also when used in combination with an α1-adrenergic receptor blocker, a 5α-reductase inhibitor, an antiandrogen drug, a β2-adrenergic receptor agonist, a phosphodiesterase V inhibitor, a plant preparation, an amino acid preparation, a herbal medicine, an intravesical instillation or detrusor injection therapy, a β3-adrenergic receptor agonist, a serotonin-norepinephrine reuptake inhibitor, a selective serotonin reuptake inhibitor, a selective norepinephrine reuptake inhibitor, a tricyclic antidepressant drug, an α1-adrenergic receptor agonist, a female hormone replacement therapy, a surgical therapy, a urinary bladder intima protecting agent, an antiallergic drug, an antihistamine drug, a steroid or bladder distention. [0013] Examples of α1 receptor blockers include tamsulosin, naftopidil, prazosin, terazosin, urapidil, indoramin, alfuzosin, doxazosin, silodosin, pharmaceutically acceptable salts thereof and the like.

Examples of 5α-reductase inhibitors include finasteride, dutasteride, pharmaceutically acceptable salts thereof and the like.

Examples of antiandrogen drugs include cetrorelix pamoate, ozarelix, teverelix, leuprorelin, chlormadinone acetate, gestonorone caproate, allylestrenol, pharmaceutically acceptable salts thereof and the like.

Examples of phosphodiesterase V inhibitors include tadalafil, vardenafil, sildenafil, UK-369003, pharmaceutically acceptable salts thereof and the like.

Examples of selective α1-adrenergic receptor agonists include phenylpropanolamine, ephedrine, methyl ephedrine, midodrine, pharmaceutically acceptable salts thereof and the like.

Examples of α1-adrenergic receptor blockers include tamsulosin, naftopidil, prazosin, terazosin, urapidil, indoramin, alfuzosin, doxazosin, silodosin, pharmaceutically acceptable salts thereof and the like.

Examples of selective serotonin reuptake inhibitors include paroxetine, sertraline, fluoxetine, fluvoxamine, pharmaceutically acceptable salts thereof and the like.

Examples of selective norepinephrine reuptake inhibitors include nisoxetine, reboxetine, pharmaceutically acceptable salts thereof and the like.

Examples of selective serotonin-norepinephrine reuptake inhibitors include duloxetine, pharmaceutically acceptable salts thereof and the like.

Examples of antiandrogen drugs include tadalafil, vardenafil, sildenafil, UK-369003, pharmaceutically acceptable salts thereof and the like.

Examples of α1-adrenergic receptor agonists include phenylpropanolamine, ephedrine, methyl ephedrine, midodrine, pharmaceutically acceptable salts thereof and the like.

Examples of α1-adrenergic receptor blockers include tamsulosin, naftopidil, prazosin, terazosin, urapidil, indoramin, alfuzosin, doxazosin, silodosin, pharmaceutically acceptable salts thereof and the like.

Examples of selective norepinephrine reuptake inhibitors include nisoxetine, reboxetine, pharmaceutically acceptable salts thereof and the like.

Examples of 5α-reductase inhibitors include finasteride, dutasteride, pharmaceutically acceptable salts thereof and the like.

Examples of selective serotonin reuptake inhibitors include paroxetine, sertraline, fluoxetine, fluvoxamine, pharmaceutically acceptable salts thereof and the like.

Examples of selective norepinephrine reuptake inhibitors include nisoxetine, reboxetine, pharmaceutically acceptable salts thereof and the like.

Examples of α1-adrenergic receptor agonists include phenylpropanolamine, ephedrine, methyl ephedrine, midodrine, pharmaceutically acceptable salts thereof and the like.

Examples of α1-adrenergic receptor blockers include tamsulosin, naftopidil, prazosin, terazosin, urapidil, indoramin, alfuzosin, doxazosin, silodosin, pharmaceutically acceptable salts thereof and the like.

Examples of selective serotonin reuptake inhibitors include paroxetine, sertraline, fluoxetine, fluvoxamine, pharmaceutically acceptable salts thereof and the like.

Examples of selective norepinephrine reuptake inhibitors include nisoxetine, reboxetine, pharmaceutically acceptable salts thereof and the like.

Examples of α1-adrenergic receptor agonists include phenylpropanolamine, ephedrine, methyl ephedrine, midodrine, pharmaceutically acceptable salts thereof and the like.
[0018] A therapeutic agent for lower urinary tract symptom of the present invention comprises a combination of (A) a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence, a therapeutic agent for interstitial cystitis/painful bladder syndrome or the like and (B) the compound A or the like, and may be any agent that allows (A) a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence, a therapeutic agent for interstitial cystitis/painful bladder syndrome or the like and (B) the compound A or the like to be combined at the time of administration. Therefore, provided that it allows (A) a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence, a therapeutic agent for interstitial cystitis/painful bladder syndrome or the like, and (B) the compound A or the like to be combined at the time of administration, the pharmaceutical composition of the present invention may be a single preparation obtained by concurrently formulating (A) a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence, a therapeutic agent for interstitial cystitis/painful bladder syndrome or the like and (B) the compound A or the like, or may be a combination of at least two different preparations obtained by preparing (A) the compound A or the like and (B) a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence, a therapeutic agent for interstitial cystitis/painful bladder syndrome or the like as separate preparations.

The dosage form is not particularly limited; examples include (a) administration as a composition comprising both (A) a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence, a therapeutic agent for interstitial cystitis/painful bladder syndrome or the like and (B) the compound A or the like, that is, as a single preparation, (b) concurrent administration via the same route of administration of two different preparations obtained by preparing (A) a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence, a therapeutic agent for interstitial cystitis/painful bladder syndrome or the like and (B) the compound A or the like as separate preparations, (c) administration via the same route of administration at a time interval of two different preparations obtained by preparing (A) a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence, a therapeutic agent for interstitial cystitis/painful bladder syndrome or the like and (B) the compound A or the like as separate preparations (for example, administration in the order of (A) a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence, a therapeutic agent for interstitial cystitis/painful bladder syndrome or the like, and (B) the compound A or the like, or administration in the reverse order), (d) concurrent administration via different routes of administration of two different preparations obtained by preparing (A) a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence, a therapeutic agent for interstitial cystitis/painful bladder syndrome or the like, and (B) the compound A or the like as separate preparations, (e) administration via different routes of administration at a time interval of two different preparations obtained by preparing (A) a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence, a therapeutic agent for interstitial cystitis/painful bladder syndrome or the like and (B) the compound A or the like as separate preparations (for example, administration in the order of (A) a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence, a therapeutic agent for interstitial cystitis/painful bladder syndrome or the like and (B) the compound A or the like be co-present in the body for a time sufficient to ameliorate a lower urinary tract symptom.

[0019] The present invention encompasses a commercial package comprising a combination agent consisting of a combination of (A) a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence, a therapeutic agent for interstitial cystitis/painful bladder syndrome or the like and (B) the compound A or the like, and a printed matter concerning the combination agent stating that the combination agent can be used, or should be used, for the treatment of lower urinary tract symptoms; a commercial package comprising a pharmaceutical composition
comprising a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence, a therapeutic agent for interstitial cystitis/painful bladder syndrome or the like, and a printed matter concerning the pharmaceutical composition stating that the pharmaceutical composition can be used, or should be used, for the treatment of lower urinary tract symptoms with the compound represented by the formula (1) or the like; and a commercial package comprising (A) a pharmaceutical composition comprising the compound A or the like and (B) a printed matter concerning the pharmaceutical composition stating that the pharmaceutical composition can be used, or should be used, for the treatment of lower urinary tract symptoms.


[0021] A therapeutic agent for lower urinary tract symptom of the present invention, when used for treatment, can be administered as a pharmaceutical composition orally or non-orally (for example, intravenous, subcutaneous, or intra-muscular injection, topical, transrectal, transdermal, or transnasal). Examples of compositions for oral administration include tablets, capsules, pills, granules, powders, solutions, suspensions and the like; examples of compositions for non-oral administration include aqueous or oily agents for injection, ointments, creams, lotions, aerosols, suppositories, plasters and the like. These preparations are prepared using conventionally known techniques, and can contain a non-toxic, inert carrier or additive in common use in the pharmaceutical field.

[0022] The dose of a therapeutic agent for lower urinary tract symptom of the present invention varies depending on the compound, as well as on the patient disease, age, body weight, sex, symptoms, route of administration and the like; usually, for an adult (weight 50 kg), each of a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence or a therapeutic agent for interstitial cystitis/painful bladder syndrome, and the compound A, is administered at 0.01 to 3000 mg/day, preferably 0.1 to 2550 mg/day, once or in two or three divided doses a day. The same can also be administered once per several days to several weeks.

Examples

[0023] The present invention is hereinafter described more specifically by means of the following reference examples, working examples and test examples, to which, however, the present invention is not limited. The compound names shown in the following reference examples and working examples do not always conform to the IUPAC Nomenclature. While abbreviations are sometimes used for the sake of simplifying the description, these abbreviations have the same definitions as those given above.

Examples

Test Example 1: Action of the compound A on C-fiber activation

[0024] This test was performed using male SD strain rats at 6 to 7 weeks of age after birth. The animals were reared in metal cages, and allowed to take food (CE-2; CLEA Japan) and water ad libitum. Rat spinal cord was dissected under halothane anesthesia. DRG tissue was removed from the spinal cord under a stereoscopic microscope, and recovered into an ice-cooled culture dish containing DMEM. The DRG tissue was digested Rat spinal cord was dissected under halothane anesthesia. DRG tissue was removed from the spinal cord under a stereoscopic microscope, and recovered into an ice-cooled culture dish containing DMEM. The DRG tissue was digested

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Examples

Test Example 1: Action of the compound A on C-fiber activation

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On the day after the start of cultivation, the DRG neurons were loaded with 5 μM DiBAC₄ (3) in the presence of 5% gaseous carbon dioxide at 37°C for 1 hour or more. Thereafter, the neurons were transferred to an assay buffer solution (pH 7.3; 10 mM HEPES, 145 mM NaCl, 5 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂, 10 mM Glucose), and the fluorescence intensity of each DRG neuron was measured using the image analytical system AQUACOSMOS (Hamamatsu Photonics). When small DRG neurons were selected and stimulated with 60 mM high-concentration K solution (pH 7.3; 10 mM HEPES, 90 mM NaCl, 60 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂, 10 mM Glucose), a rise in membrane potential was observed. When the 60 mM high-concentration K solution was replaced with the assay buffer solution, the transiently-elevated membrane potential fell rapidly. When the same was again stimulated with the 60 mM high-concentration K solution, a rise in membrane potential was observed with high reproducibility. Compared to the first rise in membrane potential (∆F/F) as 100%, the ratio of the second rise in membrane potential was 72±3% (control). Compound A (3 μM) was pretreated between the 1st and 2nd stimulations.

The effect of the compound A on the rise in membrane potential when used alone is shown in Fig. 1. With the pretreatment with the compound A (3 μM), the rise in membrane potential (∆F/F) was suppressed to 66±6%.

It is seen that the compound A has a suppressing effect on C-fiber activation when used alone.
Test Example 2: Combination effect with α₁-adrenergic receptor blocker

[0025] This test was performed using male SD strain rats at 6 to 7 weeks of age after birth. The animals were reared in metal cages, and allowed to take food (CE-2; CLEA Japan) and water ad libitum.

Rat spinal cord was dissected under halothane anesthesia. DRG tissue was removed from the spinal cord under a stereoscopic microscope, and recovered into an ice-cooled culture dish containing DMEM. The DRG tissue was digested using 0.25% trypsin and 0.38% collagenase, and DRG neurons were isolated. The DRG neurons were seeded to a cover glass coated with Poly-L-Lysine and laminin, and cultured.

On the day after the start of cultivation, the DRG neurons were loaded with 5 μM DiBAC₄ (3) in the presence of 5% gaseous carbon dioxide at 37°C for 1 hour or more. Thereafter, the neurons were transferred to an assay buffer solution (pH 7.3; 10 mM HEPES, 145 mM NaCl, 5 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂, 10 mM Glucose), and the fluorescence intensity of each DRG neuron was measured using the image analytical system AQUACOSMOS (Hamamatsu Photonics). When small DRG neurons were selected and stimulated with 60 mM high-concentration K solution (pH 7.3; 10 mM HEPES, 90 mM NaCl, 60 mM KCl, 2 mM CaCl₂, 1 mM MgCl₂, 10 mM Glucose), a rise in membrane potential was observed. When the 60 mM high-concentration K solution was replaced with the assay buffer solution, the transiently-elevated membrane potential fell rapidly. When the same was again stimulated with the 60 mM high-concentration K solution, a rise in membrane potential was observed with high reproducibility. Compared to the first rise in membrane potential (∆F/F) as 100%, the ratio of the second rise in membrane potential was 72 ± 3% (control). The drug was treated between the 1st and 2nd stimulations.

The effects of naftopidil on the rise in membrane potential when used alone and when used in combination with the compound A are shown in Fig. 2. With the pretreatment with naftopidil (30 μM), the rise in membrane potential (∆F/F) was suppressed to 40 ± 5%. When the compound A (3 μM) and naftopidil (30 μM) were used in combination, the rise in membrane potential (∆F/F) was suppressed to 27 ± 5%.

Next, the effects of tamsulosin when used alone and when used in combination with the compound A are shown in Fig. 3. The change in membrane potential due to the pretreatment with tamsulosin (0.1 μM) was to nearly the same extent as with the control. When the compound A (3 μM) and tamsulosin (0.1 μM) were used in combination, the rise in membrane potential (∆F/F) was suppressed to 55 ± 11.

It is evident from Fig. 2 that the compound A and naftopidil have a suppressing action on the high-concentration K-induced rise in membrane potential, that is, C-fiber activation-suppressing action. Furthermore, it is evident from Fig. 2 and Fig. 3 that the compound A has a combination effect with naftopidil and tamsulosin.

Test Example 3: Combination effect with β₃-adrenergic receptor agonist

[0026] This test is performed using male SD strain rats at 8 to 10 weeks of age after birth. The animals are reared in metal cages, and allowed to take food (CE-2; CLEA Japan) and water ad libitum.

While each rat is under halothane anesthesia, a cannula for measuring inner pressure is inserted into the urinary bladder. Four days after placement of the cannula, a cannula for drug administration is inserted into the stomach while the animal is under halothane anesthesia. The following day, while the animal is awake, physiological saline is perfused through the urinary bladder via a urinary bladder cannula at a rate of 6 mL/h for 1 hour or more. After the voiding interval has stabilized, the physiological saline is replaced with physiological saline containing 10 μM PGE₂, which is perfused for 1 hour or more. After the voiding interval has shortened and stabilized, bladder capacity is measured. Bladder capacity is calculated as the sum of voided volume and residual urine volume. Compound A and YM-178:

[0027]

![Diagram](image)

or a mixed liquid thereof is administered via an intragastric cannula. Bladder capacity is measured until 90 minutes after the administration. The bladder capacity is compared before and after the administration.

The bladder capacity increasing action is enhanced when the compound A and YM-178 are used in combination, than when each is administered alone.
Industrial Applicability

[0028] The present invention makes it possible to provide a novel useful therapeutic agent for lower urinary tract symptoms.

Claims

1. A therapeutic agent for lower urinary tract symptom comprising (+)-3-[1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl]-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof as an active ingredient.

2. A therapeutic agent for lower urinary tract symptom comprising a combination of (+)-3-[1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl]-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof, and a drug selected from the group consisting of a therapeutic agent for overactive bladder syndrome, a therapeutic agent for pollakiuria/urinary incontinence, a therapeutic agent for benign prostatic hyperplasia, a therapeutic agent for stress urinary incontinence and a therapeutic agent for interstitial cystitis/painful bladder syndrome.

3. A therapeutic agent for lower urinary tract symptom comprising a combination of (+)-3-[1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl]-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof, and a drug selected from the group consisting of an α1-adrenergic receptor blocker, a 5-α reductase inhibitor, an antiandrogen drug, a β3-adrenergic receptor agonist, a phosphodiesterase V inhibitor, a selective serotonin reuptake inhibitor, a selective norepinephrine reuptake inhibitor, a tricyclic antidepressant drug, an α-adrenergic receptor agonist, a female hormone, a urinary bladder intima protecting agent, an antiallergic drug, an antihistamine drug and a steroid.

4. The therapeutic agent for lower urinary tract symptom according to claim 2, wherein the therapeutic agent for benign prostatic hyperplasia is an α1-adrenergic receptor blocker.

5. The therapeutic agent for lower urinary tract symptom according to claim 4, wherein the α1-adrenergic receptor blocker is selected from the group consisting of naftopidil and tamsulosin.

6. The therapeutic agent for lower urinary tract symptom according to claim 2, wherein the therapeutic agent for benign prostatic hyperplasia is a 5-α reductase inhibitor.

7. The therapeutic agent for lower urinary tract symptom according to claim 2, wherein the therapeutic agent for benign prostatic hyperplasia is an antiandrogen drug.

8. The therapeutic agent for lower urinary tract symptom according to claim 2, wherein the therapeutic agent for overactive bladder syndrome is a β3-adrenergic receptor agonist.

9. The therapeutic agent for lower urinary tract symptom according to claim 8, wherein the β3-adrenergic receptor agonist is a selective β3-adrenergic receptor agonist.

10. The therapeutic agent for lower urinary tract symptom according to claim 2, wherein the therapeutic agent for overactive bladder syndrome or the therapeutic agent for benign prostatic hyperplasia is a phosphodiesterase V inhibitor.

11. The therapeutic agent for lower urinary tract symptom according to claim 2, wherein the therapeutic agent for benign prostatic hyperplasia is a plant preparation, an amino acid preparation, or a herbal medicine.

12. A combination therapy with (+)-3-[1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl]-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof, and intravesical instillation of resiniferatoxin or capsaicin or detrusor injection of botulinum toxin, for treating lower urinary tract symptoms.

13. The therapeutic agent for lower urinary tract symptom according to claim 2, wherein the therapeutic agent for stress urinary incontinence is a β2-adrenergic receptor agonist.
14. The therapeutic agent for lower urinary tract symptom according to claim 2, wherein the therapeutic agent for stress urinary incontinence is a serotonin-norepinephrine reuptake inhibitor, a selective serotonin reuptake inhibitor, or a selective norepinephrine reuptake inhibitor.

15. The therapeutic agent for lower urinary tract symptom according to claim 2, wherein the therapeutic agent for stress urinary incontinence or the therapeutic agent for pollakiuria/urinary incontinence is a tricyclic antidepressant drug.

16. The therapeutic agent for lower urinary tract symptom according to claim 2, wherein the therapeutic agent for stress urinary incontinence is an $\alpha$-adrenergic receptor agonist.

17. A combination therapy with (+)-3-{1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl}-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof, and a surgery for treating benign prostatic hyperplasia, for treating lower urinary tract symptoms.

18. A combination therapy with (+)-3-{1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl}-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof, and a female hormone replacement therapy, for treating lower urinary tract symptoms.

19. A combination therapy with (+)-3-{1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl}-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof, and a surgery for the treatment of stress urinary incontinence, for treating lower urinary tract symptoms.

20. A combination therapy with (+)-3-{1-[3-(trifluoromethoxy)benzyl]piperidin-4-yl}-4-phenyl-3,4-dihydro-2(1H)-quinazolinone or a pharmaceutically acceptable salt thereof, and an interstitial cystitis/painful bladder syndrome therapy, for treating lower urinary tract symptoms.
FIG. 3

![Bar graph showing comparisons between Control, Compound A, Tamsulosin, and Compound A + Tamsulosin groups. The graph indicates the percentage change in a parameter, ΔF/F (%).]
# INTERNATIONAL SEARCH REPORT

**International application No.**

PCT/JP2009/068763

## A. CLASSIFICATION OF SUBJECT MATTER

- C07D401/04 (2006.01)i, A61K31/517 (2006.01)i, A61K45/00 (2006.01)i, A61P13/00 (2006.01)i, A61P13/02 (2006.01)i, A61P13/08 (2006.01)i, A61P13/10 (2006.01)i, A61P43/00 (2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

- C07D401/04, A61K31/517, A61K45/00, A61P13/00, A61P13/02, A61P13/08, A61P13/10, A61P43/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

- Jitsuyo Shinan Koho 1922-1996
- Jitsuyo Shinan Tokoro Koho 1996-2009
- Kokai Jitsuyo Shinan Koho 1971-2009
- Toroku Jitsuyo Shinan Koho 1994-2009

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

- CASplus(STN), REGISTRY(STN)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tbody>
<tr>
<td>X Y</td>
<td>JP 2006-188466 A (Dainippon Sumitomo Pharma Co., Ltd.), 20 July 2006 (20.07.2006), example 1, compounds; paragraphs [0031], [0032] (Family: none)</td>
<td>1 2-11,13-16</td>
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</table>

☐ Further documents are listed in the continuation of Box C.  ☐ See patent family annex.

### Special categories of cited documents:

- **A** Document defining the general state of the art which is not considered to be of particular relevance
- **E** Earlier application or patent but published on or after the international filing date
- **I** Document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- **O** Document referring to an oral disclosure, use, exhibition or other means of publication prior to the international filing date but later than the priority date claimed
- **T** Document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- **Y** Document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- **Z** Document member of the same patent family

Date of the actual completion of the international search: 17 December, 2009 (17.12.09)

Date of mailing of the international search report: 28 December, 2009 (28.12.09)

Name and mailing address of the ISA/Authorized officer:

Japanese Patent Office

Facsimile No.

Telephone No.

Form PCT/ISA/210 (second sheet) (April 2007)
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<td>&amp; WO 2005/092321 A &amp; CA 2559646 A</td>
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<td>Y</td>
<td>JP 2003-201237 A (Takeda Chemical Industries, Ltd.), 18 July 2003 (18.07.2003), paragraphs [0111], [0112]; each example</td>
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<td>Y</td>
<td>KAPLAN, Steven A. et al, Tolterodine and Tamsulosin for Treatment of Men With Lower Urinary Tract Symptoms and Overactive Bladder: A Randomized Controlled Trial, JAMA, 2006, Vol.296, No.19, p.2319-2328</td>
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### INTERNATIONAL SEARCH REPORT

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<td>because they relate to subject matter not required to be searched by this Authority, namely: Claims 12 and 17 to 20 pertain to methods for treatment of the human body by therapy.</td>
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<td>3. ☐ Claims Nos.:</td>
<td>because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).</td>
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<td>2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.</td>
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<tr>
<td>3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:</td>
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<tr>
<td>4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:</td>
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</table>

**Remark on Protest**
- ☐ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

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REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- WO 03016299 A [0005]

Non-patent literature cited in the description

- Chapple CR. European Urology, 2006, vol. 49, 651 [0005] [0006]